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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/277,229	03/26/99	CITRON	M	A-581

021069
AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

HM12/0319

EXAMINER	
RAO,M	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 03/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/277,229	Citron et al.
Examiner	**Group Art Unit**
Manjunath N. Rao	1652

☒ Responsive to communication(s) filed on *Dec 28, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *1-9, 15, 16, and 21* is/are withdrawn from consideration

☒ Claim(s) *13 and 14* is/are allowed.

☒ Claim(s) *10-12 and 17-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-21 are still at issue and are present for examination.

Election/Restriction

2. Applicant's confirmation of election of Group II, (claims 10-14, 17-20) in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-9, 15-16, and 21 are withdrawn from further consideration by the examiner, 37 CAR 1.142(b), as being drawn to a non-elected invention.

3. Applicants' arguments filed on 12-28-00, paper No. 7, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is drawn to an isolated biologically active polypeptide encoded by a nucleic acid selected from a group consisting of several types of nucleic acids including item c) fragments of SEQ ID NO:4. However, SEQ ID NO:4 corresponds to a sequence of amino acids and not nucleic acids. Thus, it is unclear to the Examiner as to how fragments of a polypeptide can encode a polypeptide.

6. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 recites a complementary nucleic acid sequence (item h) as being capable of encoding a polypeptide. It is unclear to the Examiner as to how complementary nucleic acid sequences are capable of encoding a polypeptide. Examiner would like to point out to the applicants that they are claiming a polypeptide an not a polynucleotide.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a beta-secretase enzyme from humans, mouse and rat (SEQ ID NOs:4-

6), does not reasonably provide enablement for any beta-secretase enzyme from any or all sources. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 10 is so broad as to encompass any beta-secretase enzyme from any source or any recombinant, mutant or variant beta-secretase enzyme from any source. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of beta-secretase enzymes broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and to obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the beta-secretase enzyme of humans.

While enzyme isolation techniques and recombinant techniques are known, it is not routine in the art to screen multiple sources, multiple substitutions, or multiple modifications, as encompassed by the instant claims, and the reasonable expectation of success in obtaining the desired enzyme are limited due to the complexity of the huge number of microorganisms, animals and plants that need to be analyzed and the result of such isolation from an extremely large number of sources is unpredictable.

The specification does not support the broad scope of the claims which encompass all beta-secretase enzyme of any microorganism, plant or animal because the specification does **not** establish:(A) a rational and predictable scheme for isolation and characterization of any beta-secretase enzyme from any given source with an expectation of obtaining the desired biological activity and function; (B) regions of the protein structure which may be modified without effecting the beta-secretase enzyme activity; (C) the general tolerance of beta-secretase enzyme to modification and extent of such tolerance; and (D) the specification provides insufficient guidance as to which of the infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any beta-secretase enzyme of any microorganism or animal or plant. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

9. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 10 is directed to all polypeptides with beta-secretase activity. Claim 10 is rejected under this section of 35 USC 112 because the claim is directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue, and nucleic acids encoding such polypeptides, that have not been disclosed in the specification. No description of all such polypeptides and polynucleotides encoding such polypeptides has been provided. No information, beyond the characterization of SEQ ID NO:4-6 has been provided by applicants which would indicate that they had possession of all the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences that has been claimed, including the polynucleotide sequences encoding such polypeptides and variants and mutants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only 3 species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

10. Claims 11, 12, 18 and claims 19-20 which depend from claim 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11, 12 and 18 are directed to a genus of polypeptides with SEQ ID NOs 4, 5, 6 and their allelic variants and splice variants, derivatives or encoded DNA molecules with either SEQ ID NO:1, 2 or 3 and their allelic variants and splice variants encoding the above polypeptides.

The specification defines an "allelic variant" (see page 10) as an alternative form of the gene occupying a given locus on a chromosome of an organism. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. The specification defines a "splice variant" (see page 10) as a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript. These definitions do not provide any specific information about the structure of naturally occurring (alleles) variants or splice variants of SEQ ID NO:4, 5, 6 (i.e. where are the regions within which mutations are likely to occur) nor discloses any function for naturally occurring variants. There

is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:4-6 relates to the structure of any naturally occurring allele or splice variant. The general knowledge in the art concerning alleles and splice variants does not provide any indication of how one allele or splice variant is representative of unknown alleles and splice variants. The nature of alleles/splice variant is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others. The genus of polypeptides and DNAs that encode such polypeptides that comprise the claimed invention is a large variable genus. Therefore, many structurally unrelated polypeptides and DNAs encoding such polypeptides are encompassed within the scope of these claims. The specification discloses only three species of the claimed genus (i.e the polypeptide sequence with SEQ ID NO:4, 5, and 6) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102/103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 and 17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chrysler et al. (WO 9640885, dated 12-19-1996) in view of the high level of knowledge in the art of molecular biology. Claims 10 and 17 in this instant application are drawn to a polypeptide produced by culturing a host cell in a suitable medium, wherein the host cell comprises a nucleic acid molecule encoding a biologically active beta secretase, and isolating the polypeptide from the medium (claim 10) and a composition comprising the above polypeptide with a pharmaceutically acceptable carrier.

Chrysler et al. teach an isolated and purified polypeptide with beta-secretase capable of cleaving beta-amyloid precursor protein. However, the patentability of a product claimed in a product by process formate is determined by the properties of the product. The only limitation on the product itself is that it have beta-secretase properties. The polypeptide of Chrysler et al.

already has this property. Furthermore, while Chrysler et al. do not teach a host cell comprising a nucleic acid encoding the beta-secretase polypeptide with the high level of knowledge existing in the art of sequencing proteins for amino acid sequence determination and the method of making a transformant in the art of molecular biology, it would have been obvious to one of ordinary skill in the art to use the purified protein of Chrysler et al., find the amino acid sequence and use such information to clone the gene (polynucleotide) encoding the protein and transform a host cell such that culturing the host cell would yield the beta-secretase polypeptide. One of ordinary skill in the art would be motivated to do this in order to produce the beta-secretase in large amounts by recombinant methods due to its novel activity of cleaving beta-amyloid precursor protein which has been implicated in human dementia. One would have a reasonable expectation of success since Chrysler et al. provide a purified beta-secretase protein and the art (of molecular biology) teaches a reliable and time-tested method that has been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In response to the above rejection in the previous Office action, applicants have traversed that Chrysler et al. could not have made the claimed invention obvious at the time it was made as Chrysler et al. provide no amino acid sequence or DNA sequence for the beta-secretase enzyme. Applicants argue that without such information , the skilled artisan could not have prepared the compounds of claims 11 and 17-20 as these claims require the full or partial sequence of SEQ ID NO:4. Examiner agrees with the above argument by the applicants. However, the above rejection still applies to broad claims 10 and 17 wherein there are no requirements of either DNA or amino acid sequence information. Hence the rejection is maintained with respect to 10 and 17.

Allowable Subject Matter

12. Claims 13-14 are allowable.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao

March 19, 2001

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600